The Ever-Changing Landscape of Rotavirus Serotypes

Miguel O'Ryan, MD

Abstract: Rotavirus is a double-stranded RNA virus that is characterized by substantial genetic diversity. The various serotypes of rotavirus have been determined by the presence of neutralizing epitopes on the outer capsid of the protein shell. At present, 5 rotavirus serotypes (G1, G2, G3, G4, G9) are the predominant circulating strains, accounting for approximately 95% of strains worldwide, although there is considerable geographic variability. Incidence rates for various serotypes also vary temporally with seasonal and year-to-year fluctuations. Unusual serotypes are generally uncommon, but new serotypes can emerge. In particular, G9[P8], a reassortment virus, was first identified in 1983 and in the last 10 to 15 years has become widely distributed worldwide. Indeed, G9[P8] has become highly prevalent in many countries in Europe and Australia, with somewhat lower incidence rates in South America, Africa, and Asia. The heterogeneity and ever-changing epidemiology of rotavirus underscores the need for continued surveillance to ensure that vaccination programs provide optimal protection.

Key Words: rotavirus, gastroenteritis, serotype, ribose nucleic acid virus, epidemiology

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Rotavirus is a double-stranded RNA virus from the *Reoviridae* family.[1] The virus is composed of 3 protein shells: (1) an outer capsid, (2) an inner capsid, and (3) an internal core that surrounds segments of double-stranded RNA.[2] There are 7 rotavirus groups (A through G) that are determined by the antigenic specificities of proteins encased in the triple-layer capsid.[1] Of these, Group A is responsible for most endemic human disease.[3] There are also various subgroups and serotypes with serotyping based on the presence of neutralizing epitopes on outer capsid proteins (ie, VP4 and VP7).[3] VP4 is designated as the P antigenic protein because it is cleaved by the protease trypsin at the intestinal level and VP7 is designated as the G antigenic protein because it is a glycosylated structure.[2,3] These proteins have been considered relevant for the development of a rotavirus vaccine because in vitro and animal-based studies indicate that they are targets for neutralizing antibodies that provide serotype-specific and, in some cases, cross-reactive protection.[2]

EPIDEMIOLOGY OF COMMON CIRCULATING SEROTYPES

Rotaviruses are characterized by substantial diversity; there are at least 42 different G/P strains with different serotype combinations.[2] However, 5 serotypes (G1[P8], G2[P4], G3[P8], G4[P8], and G9[P8]) are the predominant circulating rotavirus G/P serotypes.[2,4,5] However, there is substantial temporal and geographic variability in the epidemiology of rotavirus serotypes, and multiple serotypes can cocirculate within the same region.[2,5] Serotypes can also vary in different regions, even within the same country. Further, the incidence of serotypes can fluctuate from year to year within the same region. For example, Clark et al[6] followed the prevalence of rotavirus strains in Philadelphia between 1994 and 1999. As shown in Figure 1,[6] the predominant circulating strain varied significantly over the 5 seasons. In 1994 to 1995, G3[P8] strains predominated. G9[P8] comprised more than 50% of cases during a G9 outbreak in the 1995 to 1996 rotavirus season. In 1996 to 1997 and 1997 to 1998 most disease was caused by G1[P8], and in 1998 to 1999 G1[P8] and G2[P4] were each responsible for approximately 50% of infections.[6]

Rotavirus also exhibits a distinct seasonality, particularly in temperate climates. In the United States, activity usually peaks in the Southwest in November/December, spreading north and east and reaching the northeastern states by April and May.[4,7] Figure 2 summarizes the distribution of rotavirus serotypes according to continents during a prolonged surveillance period of approximately 15 years.[5] The distribution describes the global distribution of human group A rotavirus G and P types from 1989 through 2004, based on the results of 124 studies from 52 countries. Although the 5 most common rotavirus serotypes (G1–G4 and G9) were responsible for approximately 95% of infections worldwide, there are substantial geographic differences. For example, G1[P8] was responsible for more than 70% of infections in North America, Australia, and Europe but ≤30% of infections in South America, Asia, and Africa. G2[P4] was common in South America (23%) and Asia (13%), whereas G3[P8] was common in Africa (21%).[5]

EMERGING SEROTYPES

Unusual serotypes rise and fall in many parts of the world during limited time periods, but because trends could change, they require continued monitoring. Overall, strains that are considered unusual represent only 4.9% of isolates.[5] These unusual P–G combinations likely represent naturally occurring reassortments of the various human rotavirus genotypes, reassortments between human and animal strains, or direct transmission from animals to human. Notably, unusual serotypes were more common in Africa (27%), Asia (14%), and South America (11%) compared with North America, Europe, and Australia (5%, 1.4%, 0.1%, respectively). For example, G8 strains—mainly G8[P4] and G8[P6]—have been increasingly reported in Africa since the mid-1990s, accounting for approximately 13% of infections. However, to date, these strains have rarely been reported outside of Africa. Similarly, G5[P8] has been reported almost exclusively in South America.[5] G12 strains with both P8 and P6 VP4 antigenicity are being increasingly recognized worldwide, including in the United States.[8]

The relatively high frequency of unusual serotypes in some geographic regions suggests that these serotypes may have genetic stability and the potential to spread among the population; but whether they will sustain in a given population over time—indicating that they are fit for human intestinal cell receptors—requires further monitoring. In addition, most epidemiologic surveys have noted the occurrence of nontypeable rotavirus strains. This is likely due to the ability of the virus to undergo constant genetic variation via sequential point mutations (ie, antigenic drift), genetic reassortment (ie, antigenic

From the Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Santiago, Chile.

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Address for correspondence: Miguel O'Ryan, MD, Institute of Biomedical Sciences, Faculty of Medicine, University of Chile, Avda Independencia 1027, Santiago, Chile. E-mail: moryan@med.uchile.cl.

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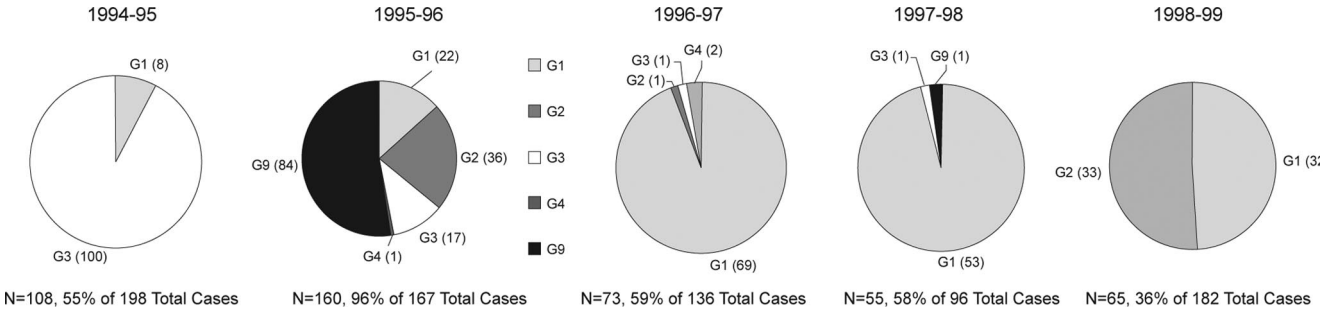

FIGURE 1. Prevalence of rotavirus strains in Philadelphia from 1995 to 1999. Reprinted with permission.[6]

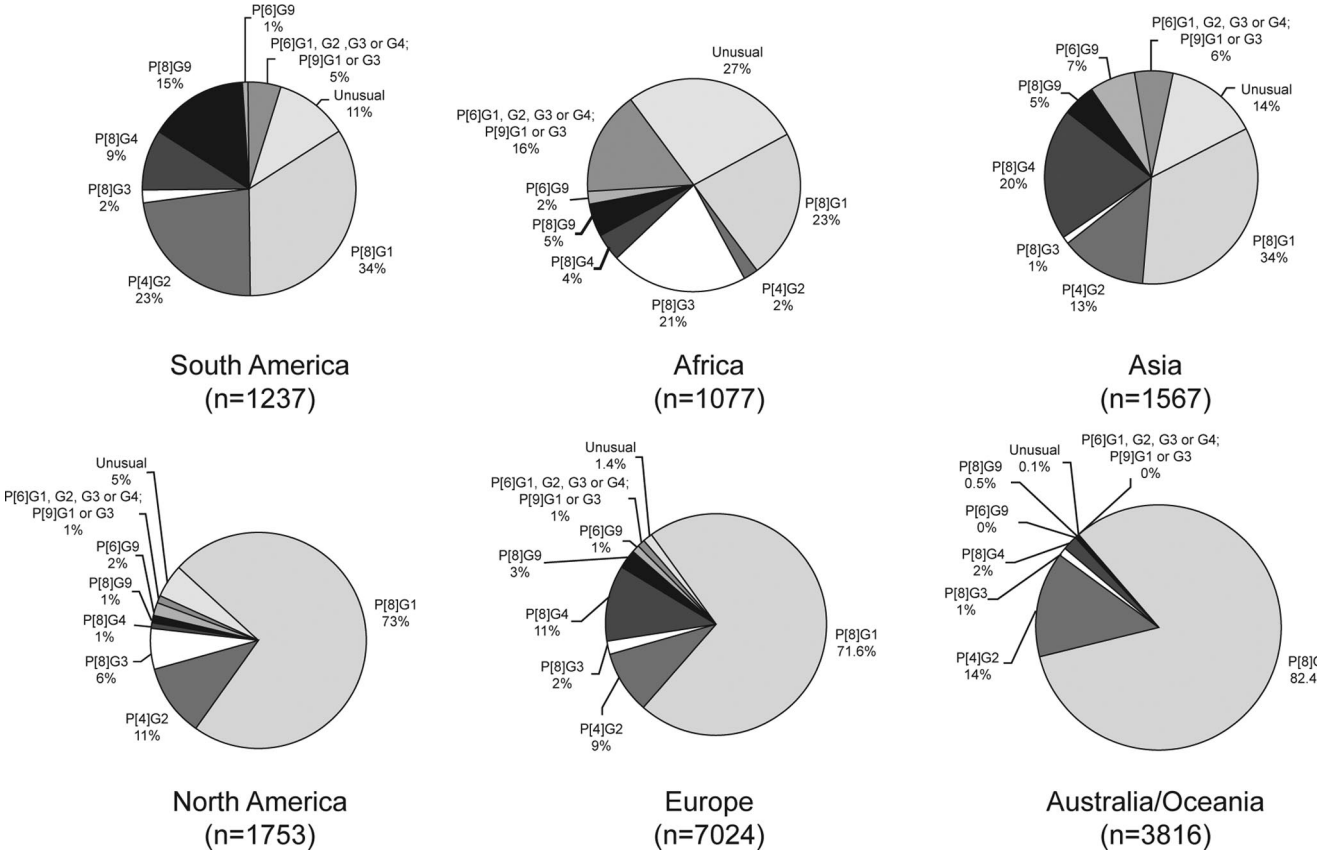

FIGURE 2. Geographical distribution of rotavirus serotypes. Reprinted with permission.[5]

shift), genomic rearrangement, or intragenic recombination. The incidence rate of nontypeable strains in various surveys is dependent on the type of assay used with the use of enzyme immunoassay generally associated with higher rates of nontypeable strains compared with studies that use reverse transcription polymerase chain reaction (RT-PCR) assays. Nevertheless, even studies that use enzyme immunoassay, RT-PCR, and probe hybridization in combination report rates of 8% to 27% for nontypeable strains. Again, if these strains will prevail in a given population, it will depend on their capacity to adapt to human intestinal cell receptors.[5]

THE EMERGING G9 SEROTYPE

The G9 strain, usually in combination with P8 or P6, is the only "new" serotype that has gained epidemiological relevance in the past years. G9 as a cause of diarrhea was first identified in Philadelphia, Pennsylvania, in 1983 and was relatively rare until the last 10 to 15 years.[6,9,10] The G9 serotype has subsequently become ubiquitous in the United States and other countries and is now the fourth most common strain worldwide, accounting for 4.1% of infections.[5,6] G9 strains have been documented in a number of epidemiologic studies conducted in the past 10 years. G9 has been identified in Australia,[11–16] Ireland,[17] Spain,[18] Sweden,[19] Hungary,[20,21] Bulgaria,[22] Slovenia,[23] Italy,[24,25] North America,[26] South America,[27,28] Africa,[29,30] Saudi Arabia,[31] and Asia.[10,32] Rates of G9 in any given year can fluctuate widely.[6,11–16,33] This is illustrated in Table 1,[11–16,34,35] which presents rates reported in Australia, a country that has conducted extensive rotavirus surveillance for many years.

TABLE 1. Nationwide Incidence of Rotavirus Serotypes in Australia From 1999 to 2007[11–16,34,35]

Time Frame	Serotype*				
	G1	G2	G3	G4	G9
1999–2000	58%	2%	<1%	2%	10%
2000–2001	50%	13%	<1%	10%	18%
2001–2002	39%	2%	0	2%	40%
2002–2003	11%	1%	2%	<1%	75%
2003–2004	40%	17%	26%	<1%	12%
2004–2005	48%	48%	1%	37%	7%
2005–2006	40%	1%	15%	23%	15%
2006–2007	37%	<5%	23%	0	31%

*Percentages do not equal 100% because some serotypes could not be assigned and some were mixed reactions.

SUMMARY AND CONCLUSIONS

Rotavirus is a common gastrointestinal pathogen that produces considerable morbidity and mortality. Currently, 5 serotypes (G1–G4, G9) predominate, accounting for almost 95% of strains worldwide. Circulating strains vary both regionally and temporally, with substantial year-to-year, seasonal, and geographic variability. In addition, reassortments of the various human rotavirus genotypes can potentially allow new serotypes to emerge, although new serotypes would have to be fit for human intestinal receptors to prevail over time. The ever-changing epidemiology of rotavirus may represent a substantial challenge to the development of effective vaccines. This emphasizes the need for long-term rotavirus surveillance to judge effectiveness of vaccines on circulating strains.

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